Haematopoietic stem cell niches: new insights inspire new questions.

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Authors: Fernando Ugarte, E Camilla Forsberg

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Public Summary:
Haematopoietic stem cell (HSC) niches are an intensely studied topic that aims at understanding the elusive cues from the microenvironment that supports HSC function in vivo. Combined with the intrinsic properties of HSCs, these signals are capable of maintaining a perfect balance of HSC quiescence and proliferation, self-renewal and differentiation to maintain haematopoietic homeostasis under drastically dynamic conditions throughout life. Nevertheless, HSC biology still suffers from many unknowns, and it is frustrating to admit that despite decade-old knowledge that adult HSCs reside primarily in the bone marrow (BM), we do not have a clear mechanistic understanding of the cues that attract them to and retain them in the BM, and we do not understand the complex inputs that enable HSC self-renewal within these niches. These gaps in understanding the basic biology of HSC regulation hamper our clinical treatment strategies. The difficulty in achieving robust ex vivo expansion of functional HSCs- considered the 'holy grail' of haematopoiesis - and inability to derive robustly engrafting HSCs from pluripotent cells means that we cannot provide a reliable supply of HSCs for all patients, although many lives could be saved and painful diseases cured if we did. We also lack protocols for specific manipulation of HSC dislodgment out of and engraftment into BM niches. Thus, more than 50 years after the first successful haematopoietic transplantation in humans, we still have to use non-specific, broadly damaging and, too often, lethal approaches to enable transplanted HSCs to engraft and thrive long term in the recipient. By comprehending the function of HSC niches, we hope to solve these issues and many more, including how extrinsic cues affect lineage output and contribute to leukaemogenesis and other haematopoietic disorders. Although many factors are involved in HSC maintenance, this manuscript will review some of the unresolved issues, using recent discoveries on the structural, cellular, and molecular regulation of HSC maintenance by extrinsic factors as the framework for discussion and future directions. These recent findings made major strides towards understanding extrinsic regulation of HSCs, with strong support for vascular regulation of HSC maintenance. It is important, however, to also consider the significant evidence for other cell types in HSC function, including adipocytes and OBCs. Cooperation of BM cells to create one unique HSC niche has not yet been distinguished from the possibility of different niches with different functions, but the notion that HSCs are regulated by a combination of complex factors is steadily growing.

Scientific Abstract:
Haematopoietic stem cell (HSC) niches provide an environment essential for life-long HSC function. Intense investigation of HSC niches both feed off and drive technology development to increase our capability to assay functionally defined cells with high resolution. A major driving force behind the desire to understand the basic biology of HSC niches is the clear implications for clinical therapies. Here, with particular emphasis on cell type-specific deletion of SCL and CXCL12, we focus on unresolved issues on HSC niches, framed around some very recent advances and novel discoveries on the extrinsic regulation of HSC maintenance. We also provide ideas for possible paths forward, some of which are clearly within reach while others will require both novel tools and vision.